was filed November 4, 1996 as a National Stage filing under 35 USC §171 based on PCT/IB95/00264, which was filed internationally on April 13, 1995 as a Continuation-In-Part of Application No. 08/239,094 filed May 6, 1994, now abandoned.

Claims 72 and 125 have been amended by deleting the phrase "after ingestion" as the correction of a typographical error made when amending the claims in an earlier response. The phrase refers to an in vivo limitation, hence makes no sense in the context of a claim that was drafted to describe an in vitro test.

Claims 72-148 are currently pending in the application (it is assumed that the citation of claims 77-148 as pending in item 4 on the summary page was a typographical error).

Claims 72 and 125 have been currently amended.

Claims 72-76, 80-86, 93-129, 133-139, and 146-148 stand rejected, as explained in detail below.

Claims 77-79, 87-92, 130-132, and 140-145 were previously withdrawn as being directed to a non-elected species.

Claims 72, 96, and 125 are independent.

Claims 72-76, 80-86, 93-129, 133-139, and 146-148 stand rejected over Curatolo (US 5,605, 889), further in view of Handsfield, Urquhart (US 4,851,231), and Edgren (US 4,522,625). The Examiner stated, in pertinent part:

> Claims 72-76, 80-86, 93-130, 133-139, and 146-148 are rejected under 35 USC 103(a) as being unpatentable over Curatolo et al (US Pat. 5,605,889) in view of Handsfield et al., Urquhart (US Pat. 4,851,231) and Edgren (US Pat. 4,522,625) for the reasons of record set forth in the prior Office Action and the further reasons below.
>
> Curatolo et al. is cited for the same reasons as the prior Office action and the same is incorporated herein. Additionally, a formulation is taught wherein the average percent azithroymycin dissolved at 30 minutes was 76% (Column 11, Example1).
>
> Handsfield, Urquhart and Edgren are cited for the same reasons as the prior Office Action and the same are incorporated herein.
>
> Examiner has duly considered Applicant's arguments but deems them unpersuasive for the same reasons set forth in the prior Office Action and the further reasons below.
>
> Applicant argues that the amendment to the claims avoids the prior art. However, the prior art does teach formulations close to 70% and teaches the benefits of delaying release until the formulation reaches the intestine as opposed to the stomach which for the same reasons would motivate one to combine the prior art. "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 31 USPQ2d 1130, 1132, (Fed. Cir.

1994). The fact that Curatolo also teaches immediate release compositions does not make the claimed invention nonobvious. The claimed formulation is known or suggested by the prior art and the advantages of controlled release are known. Any adverse food effect can be easily avoided by simply taking the formulation on an empty stomach. [Office Action, pages 2-3]

Applicants' Traversal

As a preliminary matter, a brief review of the invention itself would be useful.

The invention relates to controlled release dosage forms of azithromycin, which dosage forms have an improved side effect profile. The scientific determination that underlies the invention is disclosed in the specification at page 6, lines 14-28:

> The inventors conducted a series of studies in man in which the incidence and severity of gastrointestinal side effects were assessed after dosing azithromycin intravenously, orally, duodenally (via nasoenteric intubation), and ileally (via nasoenteric intubation). The studies demonstrated that the incidence of gastrointestinal side effects is relatively low after intravenous dosing, even at doses which are equivalent to a 5.4 g oral dose. Thus, while not wishing to be limited by or to any particular theory or mechanism, the gastrointestinal side effects of orally dosed azithromycin appear to be mediated by local interactions between azithromycin and the intestinal wall. Furthermore, the nasoenteric intubation studies demonstrated that duodenal azithromycin dosing results in more severe gastrointestinal side effects than does ileal dosing. The inventors accordingly determined that dosing azithromycin in a manner which reduces exposure of the duodenum to high concentrations of the drug results in decreased gastrointestinal side effects.

As explained above, the inventors based the invention on their determination that azithromycin side effects are mediated locally, in the upper gastrointestinal (GI) tract. It was this determination that formed the basis by which the inventors solved the problem of azithromycin side effects by formulating azithromycin in a controlled release dosage form that either reduces exposure of the upper GI tract to azithromycin or avoids such exposure altogether. Prior to their clinical studies, there was no reason to formulate azithromycin in a controlled release dosage form because of its long half-life. That is, azithromycin has a long half-life of 69 hours, meaning it takes 69 hours to purge half of the azithromycin administered in a previous dose. 69 hours is a very long time relative to the 6 hour time scale of claim 72 or the one-half hour time scale of claim 96. Thus, in relation to the patentability of the instant invention, there is a fundamental issue for consideration: - - What would one of ordinary skill in the art possibly have hoped to accomplish by putting azithromycin in a dosage form that operates on a scale of several hours when azithromycin stays in the body for much, much longer, (one half still being

present after a time on the order of 70 hours), in the first place? Only Applicants, by reason of the study they disclose in their specification (and as quoted above) had motivation to formulate azithromycin in a controlled release dosage form.

Thus, prior to the inventors' clinical investigational work, there existed no basis on which to predict (1) whether GI side effects of azithromycin were mediated systemically or locally in the GI tract, or both; (2) that there even existed more sensitive and less sensitive regions of the GI tract; or (3) that sustained or delayed release dosage forms could improve the GI toleration of azithromycin.

The art cited by the Examiner does nothing to change the way one of ordinary skill in the art would have viewed azithromycin at the time the invention was made.

Curatolo teaches nothing that would lead one of ordinary skill in the art to consider azithromycin controlled release. Curatolo is related to immediate and/or fast release dosage forms, i.e., those dosage forms which release azithromycin without any mechanism for intentionally prolonging or delaying its release. It is illogical to assert a reference related to fast release (Curatolo) against an application directed to its antithesis, controlled release.

It is equally illogical to combine Curatolo, dealing as it does with fast release, with secondary references concerned with controlled release (Urquhart and Edgren) in order to support a rejection. One of ordinary skill in the art interested in controlled release dosage forms would undoubtedly dismiss Curatolo out of hand as irrelevant and/or be led away from the invention. Applicants continue to maintain that the only reason for making a rejection involving Curatolo must be based on hindsight. That is because the only thing Curatolo has in common with the instant application is that it relates to azithromycin. The dosage forms disclosed and claimed in Curatolo are otherwise not only distinct from, but opposite to the ones instantly claimed.

The Examiner commented that

> Applicant urges that the amendment to the claims avoids the prior art. However, the prior art does teach formulations close to 70% and teaches the benefits of delaying release until the formulation reaches the intestine as opposed to the stomach which for the same reasons would motivate one to combine the prior art. "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the samwe use" In re Gurley, 31 USPQ2d 1130....[Page 3, lines 4-8]

Applicants traverse the above reasoning on the following basis.

Curatolo is directed to immediate release dosage forms, as described in Applicants' comments above (incidentally, Example 1 of Curatolo relates to capsules, a dosage form excluded from his teachings; see column 3, lines 17-18). Curatolo provides no basis on which one of ordinary skill in the art would be motivated to modify his fast release teachings and make a dosage form that releases less than 70% of its contained azithromycin within one half hour. One of ordinary skill would view Curatolo for what it teaches - - fast release. One of ordinary skill would similarly view Example 1 of Curatolo for what it is - - an example outside his invention. The point is this - - How and why would one of ordinary skill be motivated to modify Curatolo's Example 1 into a controlled release dosage form when Curatolo provides no basis for doing so? How and why would one be motivated to modify the dosage form of Example 1 to release less than 76% within a half hour when Curatolo otherwise teaches fast release?

The Examiner appears to be trying to supply the missing motivation with the secondary reference Urquhart, based on the alleged Urquhart teaching that "...certain drugs such as erythromycin should not be administered to the stomach but to the intestine over time" (see the Office Action mailed on March 26, 2003, page 2, last 2 lines). This reasoning is traversed as being clearly based on hindsight. Erythromycin and azithromycin are distinct from each other, are structurally different drugs and have very different properties. For example, erythromycin has a short elimination half life and must be given 3 or 4 times daily for at least 10 days. Azithromycin has a 69 hour half life and can be given once per day for 1, 3, or 5 days. Other significant differences abound between these two different drugs. Indeed, during the prosecution of Curatolo, patentees submitted a Rule 132 declaration demonstrating many of those differences. A copy of that declaration, reproduced from Applicants' file copy, is attached hereto as Exhibit A for the convenience of the Examiner. Attention is particularly directed to Paragraph 2, reproduced immediately below:

> 2. Azithromycin is an azalide antibiotic with chemical, physical, biological and pharmaceutical properties quite different from other antibiotics, including erythromycin. Further, azithromycin is 326 times more stable than erythromycin in solution (Fiese and Steffen, Journal of Antimicrobial Chemotherapy, 1990, 25, Suppl. A. 39-47, a copy of which is attached as Exhibit A). Azithromycin differs structurally from erythromycin by having a 15-membered ring rather than a 14-membered ring. Further, azithromycin lacks the C-9 ketone of erythromycin, having instead a (methyl)amino methylene group between the C-8 and C-10 carbons. As a result of its unique chemical structure, azithroymcin has an exceptionally long elimination half-life (69 hours in humans), which permits

> successful therapy with once-daily dosing for one to five days. By contrast, erythromycin has an approximately two hour elimination half-life in humans, and must be dosed multiple times per day for many days. These elimination half-life distinctions reflect different sensitivities to metabolic enzymes in the human body, and are also reflective of differences in the chemical labilities of these two distinct antibiotics.

Clearly the declaration demonstrates numerous and significant differences between azithromycin and erythromycin, and in doing so demonstrates that no quick and easy conclusions can be drawn about azithromycin from what is known about erythromycin. The two drugs are simply too dissimilar in their behavior and their properties to make any simple, automatic conclusions. For this reason it is respectfully submitted that it is simply untenable to combine Urquhart with Curatolo, in addition to which the two are directed to cross purposes - - controlled release versus immediate/fast release.

Handsfield and Edgren, as discussed in previous responses, add nothing to Curatolo and Urquhart. Edgren is simply an example of a controlled release dosage form, but with no suggestion to control the release of azithromycin. Handsfield simply demonstrates that azithromycin is a good, effective antibiotic.

The Examiner is accordingly asked to reconsider the rejection on the basis provided above. As noted, the only reason for one to combine the references in the manner they have been combined is Applicants' own disclosure, i.e., hindsight. Further, a combination of references is improper unless the prior art suggests the combination, which is not the case here. The primary reference, Curatolo, is unrelated to controlled release and the secondary references teach nothing that would lead one of only ordinary skill in the art to modify Curatolo, particularly as the secondary references are directed to a different purpose. See In re Bond, 15 Uspq2d 1566 (Fed. Cir. 1990) in which it was held that the PTO erred in rejecting a claimed invention as an obvious combination of the teachings of two prior art references when the prior art provided no teaching, suggestion, or incentive supporting the combination. See also Smithkline Diagnostics v. Helena Laboratories Corp., 8 USPQ2d 1468, where the court stated that a challenger to the validity of a patent "cannot pick and choose among the individual teachings of assorted prior art references to recreate the claimed invention"; the challenger has the burden to show some teaching or suggestion in the references to support their use in the particular claimed combination. In the instant rejection, the Examiner has not cited any such teaching or suggestion. See also In re Mahurkar Patent Litigation, 28 USPQ2d 1801 (N.D. Ill. 1993)

where it was stated that decomposing an invention into its constituent elements, finding each element in the prior art, and then claiming it is easy to reassemble these elements into the invention is a forbidden *ex post* analysis.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

Date: June 17, 2004

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